Acta Medica et Biologica
Vol. 44, No. 4, 209-213, 1996

Granulocytosis and Lymphocytopenia in the Blood as Indicators for Drug Adverse Reaction during Calcitonin Therapy in Patients with Osteoporosis after Gastrectomy, Including a Case Report

Minoru FUKUDA[1], Soichiro YAMAMURA[2], Tadamasa HANYU[2] and Toru ABO[3]

[1]The Sakamachi Hospital, Arakawa-machi; [2]The Department of Orthopedics and [3]The Department of Immunology, Niigata University School of Medicine, Niigata, Japan

Received July 2 1996; accepted September 17 1996

Summary. **Calcitonin therapy for patients with osteoporosis after gastrectomy is widely applied. Since a drug adverse reaction of this hormone is obscure, it is unknown how long the therapy can be continued or when it should be stopped. In this clinical study, it was found that patients with such osteoporosis (even after the initiation of calcitonin therapy) had a low proportion of granulocytes and a high proportion of lymphocytes in the peripheral blood. This leukocyte pattern indicates the parasympathetic nerve dominance in the hosts. When they were treated with a single injection of calcitonin, the leukocyte pattern returned transiently to a normal pattern (i.e., an increase of granulocytes), in parallel with increases in pulse rate and blood pressure (i.e., sympathetic nerve strain). Most of these changes were reversible. One typical patient who received long-term calcitonin administration and fell victim to anorexia, insomnia, cataracts, etc. (all of which are signs of sympathetic nerve strain) is then presented. During six years, of therapy, granulocytosis and lymphocytopenia were observed beginning four years after initiation. When the calcitonin therapy was ceased, all signs disappeared in parallel with normalization of the leukocyte pattern. These results suggest that an overdose of calcitonin administration manifests itself as sympathetic nerve strain, and that the leukocyte pattern in the blood is a good indicator of such reaction.**

Key words—calcitonin, granulocytosis, lymphocytopenia, osteoporosis, gastrectomy.

Correspondence: Minoru Fukuda, M.D., The Department of Immunology, Niigata University School of Medicine, Asahimachi 1, Niigata 951, Japan.

INTRODUCTION

Patients who undergo total gastrectomy often suffer from osteoporosis due to calcium malabsorption.[1)] To improve this situation, combination therapy with calcitonin and vitamin D_3 has been carried out in such patients.[2)] However, we noticed that the continuation of such therapy sometimes induces signs of calcitonin overdose, such as cataracts, anorexia, insomnia, tachycardia, etc. It is suspected that these conditions are due to sympathetic nerve strain induced by calcitonin.[3,4)] Namely, metabolic activities in the muscle and other tissues are elevated by calcitonin. As a result, the production of calcium triprosphate, a metabolic substance which is the major component of bone, is elevated in the body. This effect of calcitonin accelerates bone formation but may also be related to a drug adverse reaction (e.g., hypercalcemia induces sympathetic nerve strain).

In recent studies by us and other investigators, the administration of calcitonin was found to have potent immunosuppressive activity in humans and mice.[5-8)] There are many reports on calcitonin receptors on lymphocytes[9,10)] and granulocytes.[11,12)] In this study, attention was focused on the levels of lymphocytes and granulocytes in the peripheral blood during calcitonin therapy in patients with osteoporosis after gastrectomy. To our knowledge, this kind of study has remained uninvestigated until present. It was demonstrated that granulocytosis and lymphocytopenia were induced after the administration of calcitonin in these patients. Usually, this effect was

reversible. However, the long-term use of calcitonin induced a drug adverse reaction. The signs of overdose did not seem to be apparent up to 30% of a lymphocyte-to-total-leukocyte ratio, but became obvious at less than 20% (our unpublished observation). We believe this leukocyte pattern is an important indicator for drug adverse reaction during calcitonin therapy. The underlying mechanism in this phenomenon may be that granulocytes carry a high level of adrenergic receptors on the cell surface.[13,14] Namely, the effect of calcitonin on the sympathetic nervous system might be the cause of granulocytosis in the peripheral blood of patients.

MATERIALS AND METHODS

Patients

Twenty-four patients (male 11 and female 13) with osteoporosis after total gastrectomy who had subsequently received combination therapy of salmon-calcitonin (Yamanouchi Seiyaku, Tokyo, Japan) and vitamin D_3 for more than 3 years were selected. In general, a sigle intramuscular injection of 10 IU calcitonin in 0.5 ml water was given once a week (or twice a month for outpatients), and vitamin D_3 (1 μg of tablet) was given every day. The patients' ages ranged from 57 to 84 years old (mean age=72.1). Twelve patients (male 11, female 1, mean age=68.7) with gastrectomy who did not have osteoporosis for 5 years after surgery were also examined as a control. A typical case (female, 78 years old) who fell victim to a drug adverse reaction is also reported. When bone mineral density was greater than 2.5 SD below the mean value of peak bone marrow mass in young normal women, patients were estimated to have osteoporosis.

Parameters examined

The total number of leukocytes and the percentages of granulocytes and lymphocytes were examined in all subjects. To determine the levels of autonomic nervous system activity, pulse rate and systolic blood pressure were measured before and after (1 h later) each injection of calcitonin during the therapy. The serum level of calcium and the bone mineral content (BMC) were also measured in patients, especially at the time when therapy was started and thereafter.

Statistical analysis

Differences in data was analyzed by a paired t-test.

RESULTS

Increase in the proportion of granulocytes and decrease in the proportion of lymphocytes in the blood after treatment with calcitonin

Patients with osteoporosis after gastrectomy who received calcitonin therapy were examined before and after (4 h later) the injection of calcitonin (10 IU) (Fig. 1). It was demonstrated that the absolute number of granulocytes ($p<0.01$) as well as that of total while blood cells (WBC) increased subsequent to calcitonin injection. The proportion of granulocytes was elevated (53→62%), but that of lymphocytes (45→35%) decreased significantly due to the treatment ($p<0.01$). The control group, which consisted of patients without osteoporosis after gastrectomy, showed a pattern comparable to those after the injection of calcitonin. This leukocyte pattern in control patients was almost the same as that of healthy subjects (data not shown). In other words, those patients with osteoporosis tended to have a decreased level of granulocytes.

To determine the effect of calcitonin on the autonomic nervous system, the pulse rate and systolic blood pressure in 5 of 24 patients (selected from those

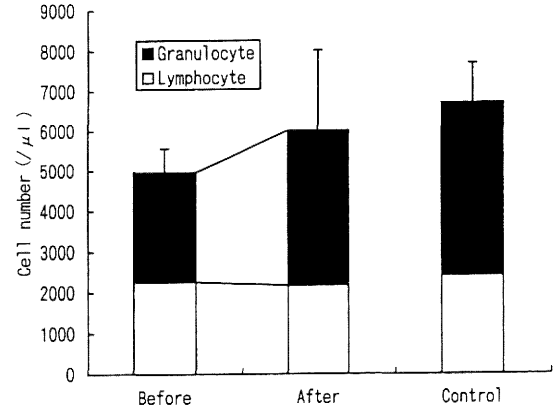

Fig. 1. Prominent increase in the absolute number and proportion of granulocytes induced by calcitonin in patients with osteoporosis and granulocytopenia. A single administration of calcitonin (10 IU in 0.5 ml water) was given to 24 patients with osteoporosis. The number and proportion of granulocytes and lymphocytes were enumerated before and after (4 h later) the administration. The control group consisted of 12 patients without osteoporosis after gastrectomy. The variation indicated by bars represents one SD from the mean value in the number of granulocytes.

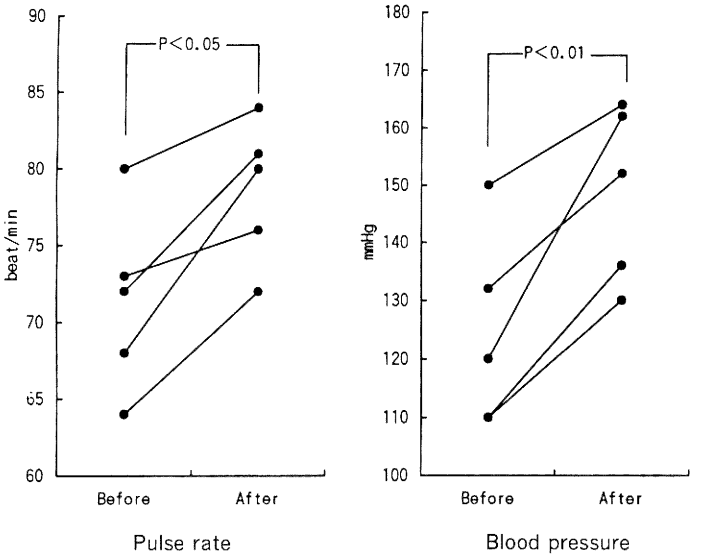

Fig. 2. Administration of calcitonin induced transiently sympathetic nerve strain. Five patients with osteoporosis were examined as to their pulse rate and systolic blood pressure before and after (1 h later) each injection of calcitonin (10 IU in 0.5 ml water). A significant elevation of pulse rate ($p<0.05$) and systolic blood pressure ($p<0.01$) was consistently observed.

in Fig. 1) were measured (Fig. 2). A significant increase in the pulse rate ($p<0.05$) and systolic blood pressure ($p<0.01$) was seen in all tested subjects (1 h after injection).

A follow-up study of one typical case showing a drug adverse reaction

In general, complaints during calcitonin therapy in patients who underwent gastrectomy are common. Such a typical case is represented, in parallel with the leukocyte pattern as shown by laboratory tests (Fig. 3). This female patient was 78 years old and had undergone gastrectomy at the age of 69 years. One year after surgery, she experienced Lumbago, estimated to be osteoporosis, and then began a combination therapy of calcitonin and vitamin D_3 which continued until recently.

Possibly because of the combination therapy of calcitonin and vitamin D_3, the level of granulocytes began to increase (>70%) and the level of lymphocytes began to decrease (<20%). From 1992 to 1993, she fell victim to cataracts and suffered from anorexia and insomnia. During this period, the serum Ca level became gradually elevated, but the bone mineral content (BMC) was not. More importantly, in parallel with the onset of granulocytosis and lymphocytopenia, the bone mineral content profoundly decreased. The level of lymphocytes then decreased by up to 10% in 1993. Since it was suspected that all of these signs had arisen from sympathetic nerve strain induced by calcitonin, its administration was ceased in 1995. All signs including even cataracts subsequently disappeared and the level of lymphocytes returned to nearly 30%.

DISCUSSION

In the present study, we demonstrated that a single injection of calcitonin immediately changed the leukocyte pattern in the blood, showing an increase in the proportion of granulocytes and a decrease in the proportion of lymphocytes. More precisely, these changes were mainly induced by an increase in the absolute number of granulocytes (note the increase in the total number of leukocytes). This variation continued for several hrs after the injection (data not shown). In other words, the levels of granulocytes and lymphocytes retutrned to the baselines thereafter. This situation was also confirmed from the fact that the level of granulocytes was very low in patients shown in Fig. 1, irrespective of calcitonin therapy. However, patients who received calcitonin therapy

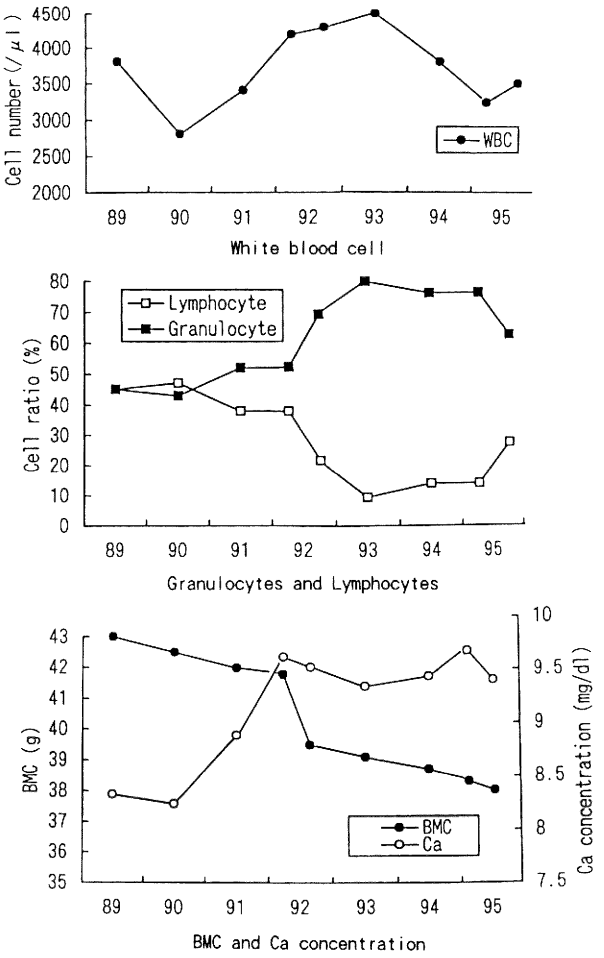

Fig. 3. Time-kinetic study of various parameters during calcitonin therapy in one typical patient who fell victim to signs of over-activation of the sympathetic nerve system. She had undergone total gastrectomy at the age of 69 years and was 78 years old in 1995. One year after surgery, she began a combination therapy of calcitonin and vitamin D_3. This therapy was ceased at the end of 1995. The abscissa indicates the year.
BMC, bone mineral content.

for long periods of time showed an irreversible effect. Namely, they showed granulocytosis and lymphocytopenia (relatively) during the therapy, with many complications due to sympathetic nerve strain. We found that all patients showing $<20\%$ lymphocytes in the blood ($n=5$) had the above-mentioned complications (in our ongoing study). We wish to emphasize that the lymphocyte level, less than 20%, may be an indicator anticipating the onset of complications beforehand.

Why does calcitonin induce granulocytosis and lymphocytopenia in the blood? It is hypothesized that sympathetic nerve strain is the main cause. There have been several reports that calcitonin induces the activation of the sympathetic nervous system.[3,4] It is also known that sympathetic nerve stimuli induce the release of calcitonin.[15,16] Therefore, all effects induced by calcitonin seem to be related to sympathetic nerve strain: 1) it increases the basic metabolism in the body and results in increases of the serum Ca level and of bone formation in conjunction with Ca absorption from the intestine aided by vitamin D_3; 2) it also induces side effects such as sympathetic nerve strain if used for a long time; and 3) it increases the levels of granulocytes which carry adrenergic receptors on the surface.[13,14] Although some lymphocytes such as NK cells and extrathymic T cells express a considerable level of adrenergic receptors, T and B cells express a lower level of adrenergic receptors (S. Suzuki et al., manuscript in preparation). On the other hand, T and B cells carry rather cholinergic receptors and decrease in number under conditions of sympathetic nerve strain. It is also related to the fact that the turnover of granulocytes from the bone marrow to the periphery is quite rapid (i.e., the life-span of granulocytes is only 2 to 3 days). In this regard, the effect of calcitonin first appears on the level of granulocytes.

Until the present, the effects of calcitonin on the body, especially on the leukocyte system, have not been totally elucidated. Since all functions induced by calcitonin are intimately related to the activation of the sympathetic nervous system,[3,4] we should pay attention to such signs. We also noticed an unexpected decrease in bone mineral content during the therapy. If we want to be aware of all such signs as early as possible, the levels of granulocytes and lymphocytes in the peripheral blood of patients might be important indicators. Since the direct indicators of sympathetic nerve strain (e.g., pulse rate, blood pressure, and serum levels of catecholamines) tend to be easily changed by physical conditions at measurement, the leukocyte pattern is both more stable and consistent in indicating the activity of the autonomic nervous system.

Acknowledgments. This work was supported by a grant-in-aid from Niigata University. We wish to thank Mrs. Kyona Kimura for preparation of the manuscript.

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